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REVIEW ARTICLE

SELECTIVE COX-2 INHIBITORS - A REVIEW

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ABSTRACT

The article discusses the mode of action and various chemical classes of selective COX-2 inhibitors which constitute a major advance in the treatment of inflammatory disorders.

INTRODUCTION

Inflammation is defined[1] as a directed tissue response to noxious and injurious, external and internal stimuli. The inflammatory stimuli can be classified[2] into four categories. These are physical stimuli, chemical stimuli, infective stimuli and immunological stimuli. Upon interaction with any one or more stimuli, the body produces a variety of substances. These substances, responsible for controlling the future course of events, are known as mediators of inflammation[1]. These mediators are also responsible for the physical symptoms of inflammatory reactions such as edema, erythema, pain and fever The mediators can be broadly classified into four categories, namely, vasoactive amines, plasma factors, arachidonic acid metabolites and lymphokines.

Chronic inflammatory conditions lead to the development of diseases including osteoarthritis, rheumatoid arthritis and other inflammatory disease[3] of the joints. Antiinflammatory drugs offer symptomatic relief in the inflammatory diseases when the underlying cause of inflammation is unidentified. The anti-inflammatory drugs can classified[4] into two categories.

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(a) **Corticosteroids:** which produce a dramatic reduction in the stiffness and paid associated with inflammatory joint diseases. However, there are several disadvantages[5] associated with long term use of corticosteroids for the treatment of chronic inflammatory diseases of the joint.

(b) **NSAIDs:** which act by inhibiting the catalytic activity of the enzymes cyclooxygenase (COX)[4]. This enzyme is responsible for catalyzing an important intermediate step in the synthesis of prostaglandins and thromboxanes from arachidonic acid[4]. Inflammatory stimuli cause a series of events which ultimately result in the conversion of arachidonic acid to prostaglandins (PG) and thromboxanes (TX) which are mediators of inflammation.

Prostaglandins, however, are physiological substances and the critical for some autocrine/ paracrine responses and for the maintenance of normal renal function, gastric mucosal integrity and hemostasis. Thus GI complications[6], including bleeding and perforation due to inhibition of prostaglandins synthesis, are responsible for a sizable number of hospitalizations[7]. Renal complications can also occur during long term use of NSAIDs[8].

This ied to further research on safer NSAIDs, based on a better understanding of their mechanism of action.

COX-ISOFORMS

An early clue to the existence of isoforms of the enzyme COX, came from a study of cell growth signaling pathways, which demonstrated increased activity of cyclooxygenase (COX) in a variety of cells after exposure to various inflammatory stimuli[9]. The two isoforms are termed as COX-1 and COX-2. COX-1 is thought to function as a physiological maintenance enzyme[10]. It produces the prostaglandins necessary for the autocrine/paracrine responses and for the maintenance of normal renal functions, integrity of gastric mucosa and hemostatis. High concentrations of COX-1 are found in platelets, vascular endothelial cells, stomach and collecting tubules in kidneys. COX-2 is virtually undetectable in most tissues under physiological conditions. It is an inducible enzyme and is induced[10] by inflammatory stimuli including interleukin-1, tumour necrosis factor, lipopolysaccharides, reactive oxygen intermediates and cAMP. Upregulation of COX-2 is regarded as a mechanism by which cellular prostaglandin concentrations are elevated in inflammation.

Recently, existence of a third isoform of the enzyme cox, termed as cox-3 is reported[11,12]. It has been suggested that cox-3 is expressed in the resolution phase of the inflammatory process. Further study on this enzyme is likely to alter the development of anti-inflammatory drugs significantly.

STRUCTURAL FEATURES OF CYCLOOXYGENASE ENZYME

Crystallographic studies on COX-1 and COX-2 as well as complexes of COX-1 and COX-2 with NSAIDs have given an insight into the structures of these enzymes[11]. When the amino acid sequence of COX-1 and COX-2 was compared, it was noted that there is 63% sequence identity. However, there exist specific biochemical differences between COX-1 and COX-2 with respect to the substrate and the inhibitor selectively. These differences are due to the substitution of isoleucine in COX-1 for valine in COX-2[13]. These valine residues are present at positions 89, 434 and 523 of the substrate binding channels and catalytic sites on COX-2[14,15]. It is the smaller size of the valine residue particularly at 523, which facilitates the binding of the drug to the receptor i.e. COX-2. The combined effect of amino acid differences at these sites, i.e. 89, 434 and 523 contributes to the larger space available for drug binding on COX-2 as compared to COX-1.

The important structural features of COX-2 can be described as follows:

COX-2 is a dimeric molecule. Each molecule consists of various domains[16]. The important domains include

(A) a catalytic domain containing heam

(B) a membrane binding domain

(C) an epidermal growth factor (EGF) domain which is N-terminal

It is the membrane binding domain that is associated with the active and binding sites for the NSAIDs. The active site of COX-2 is hydrophobic in nature with two internal hydrophilic pockets I and II, both of which possess the valine residue (positions 89 and 523). The accessibility to these pockets is controlled by the presence of valine residue at 434. The NSAIDs which occupy both the pockets, I and II, on the active sites of COX-2, are expected to possess greater specificity[15] as against drugs which bind to only one of them.

CLASSIFICATION OF COX INHIBITORS

The COX inhibitors can be classified on the basis of type of binding into the following four categories[13] :

(1) The drugs causing irreversible inhibition of both COX-1 and COX-2 e.g. Aspirin

(2) The drugs causing reversible and competitive inhibition of both COX-1 and COX-2. e.g. Ibuprofen

(3) The drugs causing slow, time dependent inhibition of COX-1 and COX-2. e.g. Flurbiprofen, Indomethacin

(4) The drugs causing highly selective inhibition of COX-2. e.g. Rofecoxib, Celecoxib.

These drugs belonging to the chemical class of diarylheterocyclics, inhibit the enzyme COX-2 in a slow, time-dependent process. The slow process is postulated to be because of the molecular complexities that accompany the penetration of the hydrophobic packets on the active site of the enzyme[16].

CHEMICAL CLASSIFICATION OF COX-2 INHIBITORS

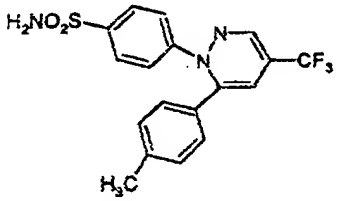
The selective COX-2 inhibitors can be classified chemically as follows

1) Diaryl heterocyclic compounds
2) Enol carboxamides
3) 2,6 ditertiary butyl phenols
4) Acetoxyphenylalkyl sulfides
5) Terphenyls
6) Miscellaneous

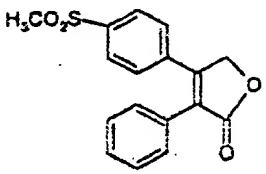
1) Diaryl heterocyclic

The diarylheterocyclic compounds remain the major and the most commonly used class of compounds in the category of selective COX-2 inhibitors[17]. Structurally, these compounds contain one heterocyclic ring in addition to two benzene rings.

The first two drugs to be introduced in clinical practice have been celecoxib[18,19] and refecoxib[20,21].

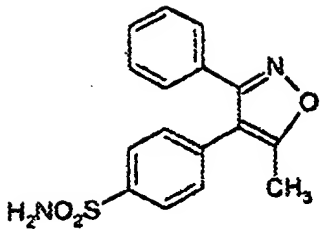


Celecoxib



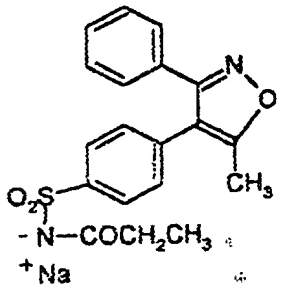
Rofecoxib

Subsequent to these two drugs, Valdecoxib[22] was identified as a potent and selective COX-2 inhibitor.



Valdecoxib

Recently a water soluble, injectable prodrug of valecoxib viz. Parecoxib[23,24] is into late phase clinical trials.



Parecoxib

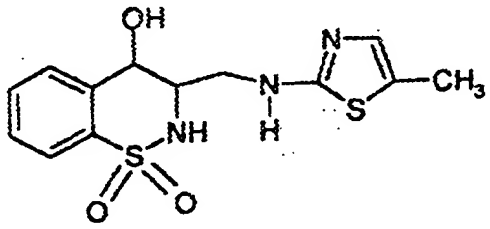
All these drugs are atleast as effective as the traditional NSAIDs in providing pain relief for acute and chronic pain conditions[25]. They are also effective in large well controlled trials in patients with rheumatoid arthritis and other chronic inflammatory conditions including osteorthritis.

It has been observed in various randomized double blind studies involving more than 5000 patients, that upper GI adverse effects are significantly lower with selective COX-2 inhibitors as compared to traditional NSAIDs[25,26]. Other adverse effects include possibility of anaphylactic reactions and precaution in patients with existing hepatic and renal diseases[21].

Rofecoxib is administered orally in a maximum daily dose of 25 mg, once a day, for osteoarthritis and 50 mg/day in single dose for acute pain. Celecoxib can be administered orally in a maximum daily dose of 200 mg, given as a single dose or as 100 mg twice a day. It is mainly used for the treatment of osteoarthritis and rheumatoid arthritis.

2) Enol carboxamides

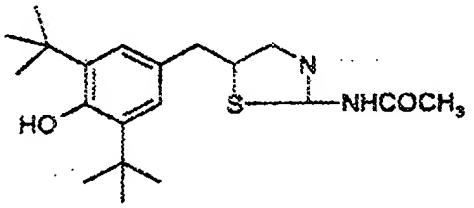
Meloxicam[27] is the best known drug of this class. Chemically it is structurally related to piroxicam, with a better selectivity profile towards COX-2 binding. It is relatively safe as compared to piroxicam.



Meloxicam

3) 2.6 ditertiarybutylphenols[28]

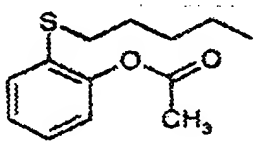
Mass screening programme identified[28] the 2,6-ditertiarybutylphenols as potent and selective inhibitors ofCOX-2. Subsequent SAR studies showed PD-138387 to be the most potent and selective cox-2 inhibitor, emerging as a novel class.



PD-138387

4) Acetoxy phenyl alkyl sulfides[29]

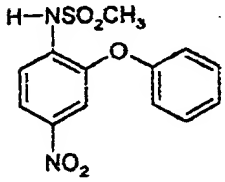
The series of these compounds was developed by modifying the structure of aspirin. These compounds bind covalently to COX-2 enzyme. Among these acetoxyphenylheptyl sulfide was most potent.



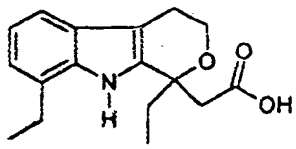
APHS

5) Miscellaneous

It has been proposed[30] that compounds containing a sulfone or sulfonamido function may display selective cox-2 inhibitory activity. With this view, when the presently used NSAIDs were evaluated[12] for their ability to selectively inhibit COX-2, it was noted that Nimesulide and Etodolac, both containing sulfonamido group, can be designated as preferential cox-2 inhibitors as against Rofecoxib which is a selective inhibitor of COX-2.



Nimesulide



Etodolac

PLANT PRODUCTS WITH COX-2 INHIBITORY ACTIVITY

Various plant products have been shown COX-2 inhibitory activity in preliminary studies. These include urosolic acid[31] from *Plantago major*, berberine[32] an isoquinoline alkaloid obtained from genera *Berberis* and *Coptis*; Rutacarpine[32], an alkaloid obtained from *Evodia rutacarpa*[33] and Resveratrol[34] an antioxidant found in grapes.

Further research[35] on these plant products is likely to result in development of some more drugs with selective COX-2 inhibitory activity.

CONCLUSION

In conclusion, it can be said that even after the initial euphoria about selective COX-2 inhibitors is over, these drugs are here to stay in clinical practice. This is mainly because of the distinct reduction in GI side effects as compared to the traditional NSAIDs. The future may see more and better selective COX-2 inhibitors to fight pain and inflammatory disorders.

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